FINAL PROFESSIONAL INFORMATION FOR IRITERO

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

IRITERO 40 mg/2 mL solution for injection

IRITERO 100 mg/5 mL solution for injection

IRITERO 300 mg/15 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IRITERO 40 mg/2 mL

One vial of 2 mL contains 34.66 mg of irinotecan as 40 mg of irinotecan hydrochloride trihydrate (40 mg/2 mL)

IRITERO 100 mg/5 mL

One vial of 5 mL contains 86.65 mg of irinotecan as 100 mg of irinotecan hydrochloride trihydrate (100 mg/5 mL)

IRITERO 300 mg/15 mL

One vial of 15 mL contains 259.95 mg of irinotecan as 300 mg of irinotecan hydrochloride trihydrate (300 mg/15 mL)

Contains sugar “sorbitol”

IRITERO contains 45 mg of sorbitol

'for full list of excipients, see section 6.1'.

3 PHARMACEUTICAL FORM.

IRITERO 40 mg/2 mL is a sterile pale yellow colour aqueous solution free from visible particles.

IRITERO 100 mg/5 mL is a sterile pale yellow colour aqueous solution free from visible particles.

IRITERO 300 mg/15 mL is a sterile pale yellow colour solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications.

IRITERO is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:

- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
- As a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2 Posology and method of administration.

Posology

Recommended Dosage:

In monotherapy (for previously treated patient):

The recommended dosage of IRITERO is 350 mg/m^2 administered as an intravenous infusion over a 30-to 90-minute period every three weeks.

In combination therapy (for previously untreated patient):

Safety and efficacy of IRITERO in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

IRITERO plus 5FU/FA in weekly schedule:

The recommended dose of IRITERO is 80 mg/m^2 administered as a weekly intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week rest.

The full dosage regimen is as follows:

IRITERO 80 mg/m^2 as a 30- to 90-minute infusion on Day 1 and then weekly for 6 weeks. Folinic acid 500 mg/m^2 i.v. as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m^2 i.v. as a 24-hour infusion, on Day 1 and then weekly for 6 weeks. The treatment is to be repeated every 7 weeks.

IRITERO plus 5FU/FA in every 2 weeks schedule:

The recommended dose of IRITERO is 180 mg/m^2 administered once every 2 weeks as an intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and 5-fluorouracil.

The full dosage regimen is as follows:

IRITERO 180 mg/m^2 i.v. as a 30- to 90-minute infusion on Day 1 only.

Folinic acid 200 mg/m^2 i.v. as a 2-hour infusion, followed by 5-fluorouracil400 mg/m^2 i.v. bolus, followed by 5-fluorouracil 600 mg/m^2 i.v. as a 22-hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days.

Repeat the cycle every two weeks.

Dosage Adjustments:

Delayed Dosing:

IRITERO should not be administered until the neutrophil count remains above 1 500 cells/mm3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of IRITERO should be delayed until there has been a full recovery of these effects, especially diarrhoea.

IRITERO should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCICTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved. This must be strictly adhered to.

At the start of a subsequent infusion of therapy, the dose of IRITERO, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20 % should be applied for IRITERO and/or 5FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4),

- non-haematological toxicity (grade 3-4).

Treatment Duration:

Treatment with IRITERO should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations:

Impaired hepatic function:

Frequent monitoring of complete blood counts should be conducted in patients with impaired liver function. Patients with a bilirubin > 1,5 times the ULN (upper limit of the normal range) should not be treated with IRITERO. In patients with a bilirubin ≤ 1,5 times the ULN range, a dose of 350 mg/m^2 IRITERO is recommended. In patients with bilirubin > 1 and ≤ 1,5 times the ULN, the risk of severe neutropenia is increased.

Elderly:

The dose should be chosen carefully in this population due to their greater frequency of decreased hepatic, renal of cardiac function.

Paediatric population:

The safety and efficacy of IRITERO in children have not been established.

Method of administration

IRITERO is administered intravenously.

Precautions to be taken before handling or administering the product.

'For instructions on dilution of the product before administration, see section 6.6.'

4.3 Contraindications

- Patients with a history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to any of the excipients listed in section 6.1.
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with IRITERO until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving IRITERO should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur (see section 4.6).
- Bilirubin > 1,5 times the upper limit of the normal range.
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant administration of azole antifungals, St. John's Wort (see section 4.5).
- Live attenuated vaccines (see section 4.5).

4.4 Special warnings and precautions for use

IRITERO should be used in patients with a WHO good performance status of less than 2 (see section 4.3).

The use of IRITERO should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered to patients under the supervision of a medical practitioner with experience in anticancer chemotherapy.

It is strongly recommended that IRITERO be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

Premedication with anti-emetic medicines are recommended in order to reduce nausea and vomiting associated with IRITERO treatment. This treatment should be started at least 30 minutes before the infusion. In all instances where the use of IRITERO is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In rare cases where it is predictable that the patient would comply poorly with the guidances for the management of side effects, a strict follow-up of the patient by the treating medical practitioner or hospitalisation is recommended.

Given the nature and frequency of adverse events, the expected benefit must be balanced in case of risk factors, especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

Delayed diarrhoea:

Apart from the diarrhoea shortly after the infusion of IRITERO, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of IRITERO and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of IRITERO. Patients should quickly inform their medical practitioner of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea:

- Patients who had a previous abdominal/pelvic radiotherapy,
- Patients with baseline leukocytosis and
- Patients with performance status ≥ 2

If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where IRITERO has been administered. After discharge from the hospital, the patients should obtain the prescribed medicines so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their medical practitioner or the department administering IRITERO that diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment is loperamide 4 mg for the first intake and then 2 mg every 2 hours. This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no case should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea in the following cases:

-Diarrhoea associated with fever,

- Severe diarrhoea (requiring intravenous hydration),

-Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).

Renal impairment:

No specific pharmacokinetic studies have been performed in patients with renal impairment.

Haematology:

Weekly monitoring of complete blood cell counts should be performed during IRITERO treatment. Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature > 38 ºC and neutrophil count ≤ 1 000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.

IRITERO administration should be delayed until the neutrophil count is ≥ 1 500 cells/mm^3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3), fever or infections associated with neutropenia, the dose of IRITERO should be reduced.

In patients who experienced severe haematologic events, a dose reduction is recommended for subsequent administration (see section 4.2). There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea, complete blood cell counts should be performed.

Liver Impairment:

Liver function tests should be performed at baseline and before each cycle. Patients with impaired liver function (bilirubin > 1,0 and ≤ 1,5 times the upper limit of the normal range [ULN] and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored, including complete blood counts. IRITERO should not be used in patients with a bilirubin > 1,5 times the ULN and the patients with bilirubin > ULN should be followed with caution. In patients with a bilirubin of < 1,5 times ULN a dose of 350 mg/m2 is recommended once every 3 weeks (see section 4.2).

Nausea and vomiting:

Prophylactic treatment with an anti-emetic is recommended before each treatment with IRITERO.

Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome:

If an acute cholinergic syndrome appears (defined as early diarrhoea and a group of symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8). These symptoms may disappear after atropine administration. Caution should be exercised in patients with asthma. In patients who experienced an acute cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of IRITERO.

Immunosuppressant effects/increased susceptibility to infections:

Administration of live or live-attenuated vaccines in patients immunocompromised by IRITERO, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients

receiving IRITERO. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Respiratory disorders:

Interstitial pulmonary disease presenting as pulmonary infiltrates may occur less frequently during IRITERO therapy. Interstitial pulmonary disease can be fatal. Risk factors possibly associated with the development of interstitial pulmonary disease include the use of pneumotoxic medicines, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during IRITERO therapy.

Extravasation:

While IRITERO is not a known vesicant, care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.

Elderly:

Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with IRITERO should be cautious in this population.

Chronic inflammatory bowel disease and/or bowel obstruction:

Patients must not be treated with [PRODUCT NAME until resolution of the bowel obstruction (see section 4.3).

Renal function:

Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhoea. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Irradiation therapy:

Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of IRITERO. Medical practitioners should use caution in treating patients with extensive prior irradiation (e.g., >25% of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan). Dosing adjustment may apply to this population (see section 4.2).

Cardiac disorders:

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8). Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimiseall modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

Vascular disorders:

Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, andarterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Others:

Concomitant administration of IRITERO with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbitone, phenytoin, apalutamide) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Women of childbearing potential and men have to use effective contraception during and up to 1 month and 3 months after treatment respectively.

This medicine contains sorbitol. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicine.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic parameters of irinotecan combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy.

Neuromuscular blocking medicines: Interaction between IRITERO and neuromuscular blocking medicines cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medicines may be antagonised. Excess acetylcholine may impair the muscle relaxant action of the non-depolarising medicines and may impair the return of normal muscle tone at the end of anaesthesia.

Antineoplastic medicines: The adverse effects of IRITERO, such as myelosuppression and diarrhoea, is expected to be exacerbated by other antineoplastic medicines having a similar adverse-effect profile.

Dexamethasone: Lymphocytopenia has been reported in patients receiving. IRITERO, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. Hyperglycaemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of IRITERO. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives: Laxative use during therapy with IRITERO is expected to worsen the incidence or severity of diarrhoea.

Diuretics: Dehydration secondary to vomiting and/or diarrhoea may be induced by IRITERO. The medical practitioner may wish to withhold diuretics during dosing with IRITERO and during periods of active vomiting or diarrhoea.

Anticonvulsants: Concomitant administration of CYP3A enzyme-inducing anticonvulsant medicines (e.g., carbamazepine, phenobarbitone or phenytoin) leads to reduced exposure to the active metabolite SN-38. Consideration should be given to starting or substituting non-enzyme inducing anticonvulsants at least one week prior to initiation of IRITERO therapy in patients requiring anticonvulsant treatment.

Azole antifungals: IRITERO clearance is greatly reduced in patients receiving concomitant azole antifungals, leading to increased exposure to the active metabolite, SN-38. Azole antifungals should be discontinued at least 1 week prior to starting [PPRODUCT NAME] therapy and should not be administered during IRITERO therapy (see section 4.3).

St. John's Wort (Hypericum perforatum): Exposure to the active metabolite of IRITERO is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be discontinued at least 1 week prior to the first cycle of IRITERO and should not be administered during IRITERO therapy (see section 4.3).

Atazanavir sulphate: Coadministration of atazanavir sulphate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of IRITERO. Atazanavir should not be used with IRITERO.

Bevacizumab: In one study, irinotecan plasma concentrations were similar in patients receiving IRITERO/5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analysed in a subset of patients.

Concentrations of SN-38 were on average 33 % higher in patients receiving IRITERO/5-FU/FA in combination with bevacizumab compared with IRITERO/5-FU/FA alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leukopenia adverse events. More dose reductions of IRITERO were reported for patients receiving IRITERO/5-FU/FA in combination with bevacizumab.

Vaccines: Yellow fever vaccine: There is a risk of fatal generalised reaction to vaccines. Concomitant use with IRITERO (see section 4.4).

Vitamin K antagonists: Increased risk of haemorrhage and thrombotic events in tumoural diseases. If vitamin Kantagonists are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Loperamide should not be given prophylactically.

4.6 Fertility, pregnancy and lactation.

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with IRITERO (see section 4.3). Women of childbearing potential and men have to use effective contraception during and up to 1 month and 3 months after treatment respectively.

Pregnancy

IRITERO is contraindicated during pregnancy as it may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of IRITERO in pregnant women. If IRITERO is used during pregnancy, or if the patient becomes pregnant, while receiving IRITERO, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

IRITERO is contraindicated during lactation**.** Patients receiving IRITERO should not breastfeed their infants.

Fertility

There are no human data on the effect of irinotecan on fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or visual disturbances, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The intensity of the major toxicities encountered with IRITERO (e.g., leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent substance and metabolite SN-38. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTION**
Infections and Infestations	Frequency	Infection
	Less frequent	Sepsis

Blood and lymphatic system disorders	Frequent	Leukopenia, *neutropenia, anaemia, Thrombocytopenia
	Frequency unknown	Peripheral thrombocytopenia with antiplatelet antibodies has been reported
Immune system disorders	Less frequent	Hypersensitivity reactions, including anaphylactic, anaphylactoid reactions.
Endocrine disorders	Less frequent	Diaphoresis, increased salvation
Metabolism and nutrition disorders	Frequent	Decrease weight, dehydration, hypovolaemia, decrease or loss of appetite
	Less frequent	hypokalaemia, hypomagnesaemia
Nervous system disorders	Less frequent	Paraesthesia, abnormal gait, confusion, headache, dizziness.
Eye disorders	Less frequent	Increased lacrimation, myosis
	Frequency unknown	Conjunctivitis, visual disturbance
Cardiac disorders	Less frequent	Hypotension, syncope, bradycardia
Vascular disorders	Frequent	Venous and arterial thromboembolic events which includes (angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep vein thrombophlebitis, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death,

		thrombophlebitis, thrombosis, vascular disorder),
	Less frequent	Hypertension, flushing
	Frequency unknown	Vasodilation
Respiratory, thoracic and mediastinal disorders	Frequent:	Dyspnoea
	Less frequent:	Rhinitis, Upper respiratory tract infection, interstitial pneumonia (see section 4.4)
Gastrointestinal disorders	Frequent	Late diarrhoea, nausea, vomiting, early diarrhoea, abdominal cramping/pain, anorexia, stomatitis, constipation, mucositis, episodes of dehydration commonly associated with diarrhoea (see section 4.4)
	Less frequent	Rectal disorder, gi monilia, intestinal obstruction, ileus or gastrointestinal haemorrhage, intestinal perforation, transient increase in amylase and lipase, anorexia, mucositis, abdominal enlargement, bloated feeling or gas, *Clostridium difficile* induced pseudo-membranous colitis, indigestion
Hepato-biliary disorders	Frequent	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Frequent	Alopecia
	Less frequent	Rash, cutaneous signs such as dry skin, pruritus,

		skin discolouration
	Frequency unknown	Sweating
Musculoskeletal and connective tissue disorders	Less frequent	Muscular contraction or cramps
Renal and urinary disorders	Less frequent	Urinary tract infection, renal insufficiency
Reproductive system and breast disorders	Less frequent	Breast pain
General disorders and administration site conditions	Frequent	Asthenia, fever, pain, neutropenic fever, mucosal inflammation
	Less frequent	Chills, malaise, infusion site reactions, extravasation, tumour lysis syndrome
	Frequency unknown	transient speech disorders
Investigations	Frequent	Increased serum creatinine, Monotherapy: transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatise, bilirubin and creatinine.
	Less frequent	Increased serum alkaline phosphate, increased

		GGTP (gamma-glutamyl transpeptidase), increase in amylase, increase in lipase

Post marketing surveillance

Infections and infestations

Pseudomembranous colitis one of which has been documented bacteriologically (*Clostridium difficile*)

- Sepsis
- Fungal infections*
- Viral infections†

Blood and lymphatic system disorders

One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

Immune system disorders:

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported.

Metabolism and nutrition disorders

- Dehydration (due to diarrhoea and vomiting)
- Hypovolaemia
- *Nervous system disorders:*

Speech disorders, generally transient in nature, have been reported; in some cases the event was attributed to the cholinergic syndrome observed during or shortly after infusion of IRITERO.

Cardiac disorders:

Myocardial ischaemic events have been observed following IRITERO therapy.

Vascular disorders

- Hypotension

Respiratory, thoracic and mediastinal disorders:

Interstitial pulmonary disease presenting as pulmonary infiltrates may occur during IRITERO therapy.

Early effects such as dyspnoea have been reported.

Hiccups have also been reported.

Gastrointestinal disorders:

Cases of intestinal obstruction, ileus, megacolon, or gastrointestinal haemorrhage, and rare cases of colitis, including typhlitis, ischaemic and ulcerative colitis have been reported. In some cases, colitis was complicated by ulceration, bleeding, ileus or infection. Cases of ileus without preceding colitis have also been reported. Cases of intestinal perforation have been reported. Cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been reported.

Hypovolaemia:

There have been cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities. Cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis.

Hepato-biliary disorders

- Steatohepatitis

- Hepatic steatosis

Skin and subcutaneous tissue disorders

- Skin reaction

Musculoskeletal and connective tissue disorders:

Muscular contraction or cramps and paraesthesia have been reported.

Renal and urinary disorders

- Renal impairment and acute renal failure generally in patients who become infected and/or volume depleted from severe gastrointestinal toxicities ‡
- Renal insufficiency‡

General disorders and administration site conditions

- Infusion site reaction

Investigations

Cases of hyponatraemia mostly related with diarrhoea and vomiting have been reported. Increases in serum transaminases (AST, ALT) in the absence of progressive liver metastasis have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of IRITERO is important. It allows continued monitoring of the benefit/risk balance of the **IRITERO**. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA **via the "6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/publications/Index/8 or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal.

Symptoms: The most significant adverse reactions reported were severe neutropenia and diarrhoea.

Treatment: There is no known antidote for IRITERO. It is recommended that the patients be hospitalised for close monitoring of vital functions and treatment of observed effects. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 26 Cytostatic medicine

Pharmacotherapeutic group: Cytostatic topoisomerase I inhibitor. ATC Code: L01CE02

5.1 Pharmacodynamic properties

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic medicine, which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines.The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA

replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found to be time dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were found not to be significantly recognised by the P-glycoprotein ^{MDR}, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumour activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinoma) and against human xenografts (Co-4 colon. adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein^{MDR} (vincristine- and doxorubicin-resistant P388 leukaemias).

Beside the antitumour activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

5.2 Pharmacokinetic properties

Absorption:

At the recommended dose of 350 mg/m^2, the mean irinotecan and SN-38 peak plasma concentrations were 7,7 µg/mL and 56 ng/mL, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/mL and 451 ng.h/mL, respectively. A large inter-individual variability in pharmacokinetic parameters is generally observed for SN-38.

Distribution

In a phase I study, in 60 patients with a dosage regimen of a 30-minute intravenous. infusion of 100 to 750 mg/m^2 every three weeks, the volume of distribution at steady state (Vss): 157 L/m^2.

In vitro, the plasma protein binding for irinotecan and SN-38 were approximately 65 % and 95 %, respectively.

Biotransformation

Mass balance and metabolism studies with 14C-labelled irinotecan have shown that more than 50 % of an intravenously administered dose of irinotecan is excreted as unchanged substance, with 33 % in the faeces via the bile and 22 % in urine. Two metabolic pathways, each representing at least 12 % of the dose, have been identified: oxidative metabolism at the terminal piperidine ring by cytochrome P450 3A enzymes which results in an aminopentanoic acid derivative (APC) and a primary amine derivate and hydrolysis by carboxylesterases into the active metabolite SN-38.

SN-38 is mainly eliminated by glucuronidation and further by biliary and renal excretion (less than 0,5 % of the irinotecan dose). Unchanged irinotecan is the major entity in plasma followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected.

Elimination

In a phase I study, irinotecan showed a biphasic or three-phasic elimination profile**.** The mean plasma clearance was 15 L/h/m^2. The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2,5 hours and the terminal phase half-life was 14,2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13,8 hours.

Irinotecan clearance is decreased by about 40 % in patients with bilirubinemia between 1,5 and 3 times the upper normal limit. In these patients a 200 mg/m^2 irinotecan dose leads to plasma irinotecan

exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal liver parameters. Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

Linearity/non-linearity:

A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three-compartment model were similar to those observed in phase I studies. All studies have shown that CPT-11 and SN-38 pharmacokinetics are independent of the administered dose, of the number of previous cycles and of the administration schedule.

Pharmacokinetic/Pharmacodynamic relationship(s):

The intensity of the major toxicities encountered with irinotecan (e.g., leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent drug and metabolite SN-38. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sorbitol
- Lactic acid

- Sodium hydroxide
- Hydrochloric acid

6.2 Incompatibilities

N/A.

6.3 Shelf life

24 months

In-use shelf life

IRITERO are subjected to 0,9 % Nacl (0,12 mg/ml Concentration), 0,9 % Nacl (2,8 mg/ml Concentration), 5 % Glucose (0,12mg/ml concentration), 5 % Glucose (2,8 mg/ml Concentration) for 24 Hrs at 2-8 °C, 3 days at 25 °C and 28 days at 5 °C

6.4 Special precautions for storage

Store at or below 25 °C and store in original package, protect from light and

moisture as well as do not freeze.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

IRITERO 40 mg/2 mL

5 ml Fiolax amber tubular glass vials, type I with 13 mm neck with 13 mm serum rubber GBB stopper with a golden yellow flip off seal.

Pack size: 1 x 10 mL

IRITERO 100 mg/5 mL

5 ml Fiolax amber tubular glass vials, type I with 13 mm neck with 13 mm serum rubber GBB stopper with a rust flip off seal.

Pack size: 1 x 10 mL

IRITERO 300 mg/15 mL

20 mL/mm Tubular type I vials with 20 mm rubber GBB stopper with a purplement flip off seal

Pack size: 1 x 20 mL

6.6 Special precautions for disposal and other handling

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of IRITERO solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation. IRITERO infusion solution should be infused into a peripheral or central vein. IRITERO should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes. If any precipitate is observed in the vials before or after reconstitution, the product should be discarded

according to standard procedures for cytotoxic agents. After dilution with either 0,9 % sodium chloride or 5 % dextrose solution, the diluted solution is stable for 24 hours under refrigeration (2 – 8 °C) and for 3 days at 25◦C and 28 days at 5◦C.

Do not admix with other medicines.

Recommendations for safe handling:

Medicine handling precautions for cytostatic medicines should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.

- IRITERO is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing IRITERO solutions.

- The work surface should be covered with disposable plastic-backed absorbent paper.

- Adequate protective gloves and clothing should be worn.

- If IRITERO solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If IRITERO solution or infusion solution should come into contact with the eyes or mucous membranes, wash immediately and thoroughly with water.

- The cytotoxic preparation must not be handled by pregnant staff.

- Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

IRITERO 40 mg/2 mL: 56/26/0829

IRITERO 100 mg/5 mL: 56/26/0830

IRITERO 300 mg/15 mL: 56/26/0831

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

11 July 2023

10 DATE OF REVISION OF THE TEXT

N/A